REMARKS

Upon entry of the foregoing amendment, claims 1-9, 11, and 13-34 are pending for the Examiner's consideration, with claims 1, 11, 13, 18, 29, and 33 being the independent claims. Claims 10 and 12 have been previously cancelled without prejudice to or disclaimer of the subject matter contained therein. Independent claims 1, 18, 29, and 33 have been amended herein to more clearly recite that the viscosity of the fluid phase of the suspension provides injectability of the composition into the host. Applicants submit that the foregoing amendments introduce no new matter. In this regard, the Examiner is referred to, for example, page 4, line 17 through page 7, line 10 of the application as originally filed.

Rejections Under 35 U.S.C. § 112 ¶ 1

The Examiner has rejected claims 1-9, 11, and 13-34 under 35 U.S.C. § 112 ¶ 1 as allegedly failing to comply with the written description requirement. As stated by the Examiner on pages 2-3 of the Office Action, "[W]hile the present specification at page 20 and 26 disclose the microparticles are suspended at a concentration of about 100 mg/ml to about 400 mg/ml, or preferably at a concentration of about 150 mg/ml to about 300 mg/ml, it appears that nowhere in the specification provides support for the limitation 'from about 175 mg/ml' and 'greater than about 300 mg/ml and less than about 400 mg/ml.' The specification does not provide adequate guidance to allow one of ordinary skill in the art to narrow the concentration from a broad range '100-400 mg/ml' down to 'greater than 300 but less than 400 mg/ml.'" For at least the following reasons, Applicants respectfully submit that the Examiner's position is contrary to Federal Circuit law, as well as to the guidance provided in M.P.E.P. § 2163.05.

As the Examiner admits, the specification as originally filed explicitly discloses a concentration range of from about 100 mg/ml to about 400 mg/ml on pages 20 and 26. What the Examiner has overlooked is the extensive disclosure throughout the specification of specific concentrations within the broad range of 100 mg/ml to 400 mg/ml. For example, Table 2 on page 14 of the application as originally filed provides data showing the effect on injectability as a function of injection vehicle viscosity, injection site, and microparticle concentration, which provides data at 160 mg/ml as well as 320 mg/ml. As another example, Table 4 on page 17 of the application as originally filed provides data showing injectability results at concentrations of

150 mg/ml and 300 mg/ml. Additional data at 300 mg/ml is provided in Table 5 on page 18 of the application as originally filed. As yet another example, page 19 of the application as originally filed describes results at concentrations of 175 mg/ml, 250 mg/ml, 150 mg/ml, and 190 mg/ml. The foregoing makes clear that the specification describes the concentration range of 100 mg/ml to 400 mg/ml, as well as specific examples at 150 mg/ml, 160 mg/ml, 175 mg/ml, 190 mg/ml, 250 mg/ml, 300 mg/ml, and 320 mg/ml within the broad range.

Applicants respectfully submit that under M.P.E.P. § 2163.05 III and *In re Wertheim*, 541 F.2d 257 (C.C.P.A. 1976), the recited concentration ranges of "from about 175 mg/ml to about 400 mg/ml" and "greater than about 300 mg/ml and less than about 400 mg/ml" meet the written description requirement. As stated in M.P.E.P. § 2163.05 III, "[W]ith respect to changing numerical range limitations, the analysis must take into account which ranges one skilled in the art would consider inherently supported by the discussion in the original disclosure." The M.P.E.P. cites to *In re Wertheim*, 541 F.2d 257 (C.C.P.A. 1976). In the *Wertheim* case, the ranges described in the specification included a range of "25%-60% and specific examples of "36% and "50%." The court found that a range of "between ***35%*** and 60%" satisfied the written description requirement. *Id.* at 265; M.P.E.P. § 2163.05 III (emphasis added). In *Wertheim,* the court found that the sub-range satisfied the written description requirement with two specific examples within the broad range, even when the lower end point of the sub-range was not a specific example. In the present case, there are seven specific examples within the broad range of 100 mg/ml and 400 mg/ml, and the lower end point of both sub-ranges is a specific example. Based on the reasoning in *Wertheim* and M.P.E.P. § 2163.05 III, Applicants respectfully submit that the recited concentration ranges of "from about 175 mg/ml to about 400 mg/ml" and "greater than about 300 mg/ml and less than about 400 mg/ml" meet the written description requirement.

As the PTO did in *Wertheim*, the Examiner appears to be arguing lack of literal "*ipsis verbis*" support for "from about 175 mg/ml to about 400 mg/ml" and "greater than about 300 mg/ml and less than about 400 mg/ml," which is not sufficient to support the rejection. As noted in *Wertheim,* the invention claimed does not have to be described in "*ipsis verbis*" in order to satisfy the description requirement of § 112. *Wertheim*, 541 F.2d at 265 (internal citations

omitted). The Examiner has not, and cannot based on *Wertheim*, carry the burden in this case as to why a description not in "*ipsis verbis*" is insufficient.

For at least all of the foregoing reasons, Applicants respectfully submit that the Examiner's rejection under 35 U.S.C. § 112 ¶ 1 for allegedly failing to meet the written description requirement cannot properly be maintained. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

The Examiner has also rejected claims 1-9, 11, and 13-34 under 35 U.S.C. § 112 ¶ 1 as allegedly not being enabled. As stated by the Examiner on page 3 of the Office Action, "the specification, while being enabling for a composition suitable for injection through a needle into a host comprising dry microparticles suspended in an injection vehicle, does not reasonably provide enablement for the microparticles suspended in injection vehicle at a concentration of from about 175 mg/ml to about 400 mg/ml." The Examiner appears to be taking the position that the specification is enabling for microparticles suspended in an injection vehicle at any concentration, but not for the recited concentration range of 175 mg/ml to 400 mg/ml. The Examiner provides no rationale why a specification enabling at any concentration becomes not enabling at the claimed concentration range.

Although the Examiner states on page 3 of the Office Action that the existence of working examples has been considered[1], the Examiner's statement on page 4 of the Office Action that "[T]he specification does not provide any guidance showing that the injectability of the composition through a needle ranging from 18-22 gauge can be achieved with the microparticles concentration as low as 175 mg/ml" is not consistent with the examples in the specification. As detailed above with the respect to the written description rejection, the specification is replete with examples showing injectability of the composition at concentrations less than 175 mg/ml, as well as concentrations between 175 mg/ml and 400 mg/ml. For example, Table 2 on page 14 of the application as originally filed provides data showing the effect on injectability as a function of injection vehicle viscosity, injection site, and microparticle

[1] As the Examiner recognizes on page 3 of the Office Acton, whether an application satisfies the enablement requirement may be considered in view of the eight "Wands factors." The Examiner provides a discussion in the Office Action of only two of the eight Wands factors, asserting nonetheless that "[A]ll of the factors have been considered." Because the Examiner has not provided a discussion of all of the factors, Applicants respectfully submit that the Examiner has not carried the burden to establish a *prima facie* case of lack of enablement.

concentration, which demonstrates successful injectability at 160 mg/ml (failure rates of 0/10 and 1/8 at high vehicle viscosity). As another example, Table 4 on page 17 of the application as originally filed demonstrates successful injectability at concentrations of 150 mg/ml (failure rate of 0/10 and 1/10 at a viscosity of 24.0 cp and 56.0 cp). In fact, the application as originally filed demonstrates successful injectability at concentrations of 150 mg/ml, 160 mg/ml, 175 mg/ml, 190 mg/ml, 250 mg/ml, 300 mg/ml, and 320 mg/ml.

The Examiner states on page 4 of the Office Action, that based on page 19 of the specification, "increasing concentration from 175 to 250 mg/ml improves the injectability," and from this appears to conclude that injectability has not been shown at 175 mg/ml. Here again the Examiner's rationale is not well founded. The sentence on page 19 actually states that "increasing the viscosity of the fluid phase of the injectable suspension decreased injection failure rate, even when microparticle concentration was raised from 175 to 250 mg/ml, at a needle size of 22 G." The complete sentence makes clear that injection failures decreased at high viscosity at concentrations of ***both*** 175 mg/ml and 250 mg/ml. There is nothing in the complete sentence from which one skilled in the art would conclude that injectability could not be achieved at a concentration of 175 mg/ml, or concentrations below 175 mg/ml; the focus of the complete sentence was on the fact that injectability could be achieved at concentrations ***above*** 175 mg/ml.

The Examiner further states on page 4 of the Office Action that "the practitioner would turn to trial and error experimentation in order to compose a composition suitable for the injection through a needle ranging from 18-22 gauge without guidance from the specification or the prior art." First, as detailed above, the specification is replete with examples showing injectability of the composition at concentrations less than 175 mg/ml, as well as in the range of 175 mg/ml to 400 mg/ml, and, as such, the specification provides guidance to one skilled in the art. Second, the test for enablement is not whether any "trial and error experimentation" was required, but rather, whether that level of experimentation was "undue" experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988); M.P.E.P. § 2164.01. As the Examiner admits on page 4 of the Office Action, "the skill of those in the art is very high, *e.g.*, Ph.D. or M.D. level technology." A high level of skill in the art means that experimentation must reach a ***higher*** threshold to be considered "undue." *Falkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006). In

sharp contrast to the Examiner's position regarding enablement, the Examiner asserts on page 6 of the Office Action that "one of ordinary skill in the art would have been motivated to, by ***routine*** experimentation determine a suitable microparticles [sic] concentration to obtain the claimed invention" (emphasis added). On the one hand the Examiner asserts that the claims are allegedly not enabled because experimentation is "undue," yet on the other hand the claims are unpatentable because the experimentation is "routine." The Examiner cannot have it both ways.

Given all of the examples in the specification showing injectability of the composition at concentrations less than 175 mg/ml, and between 175 mg/ml and 400 mg/ml, and the high level of skill in the art as defined by the Examiner, Applicants respectfully submit that the application as originally filed fully enables one skilled in the art to make and use the present invention with a concentration range of from about 175 mg/ml to about 400 mg/ml.

For at least all of the foregoing reasons, Applicants respectfully submit that the Examiner's rejection under 35 U.S.C. § 112 ¶ 1 for allegedly failing to meet the enablement requirement cannot properly be maintained. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

Rejection Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-9, 11, 13, and 15-34 under 35 U.S.C. § 103(a) as allegedly being unpatentable over WO 97/44039 ("the Francois PCT") in view of WO 95/13799 ("the Ramstack PCT"). In addition, the Examiner has rejected claim 14 as allegedly being unpatentable under 35 U.S.C. § 103(a) over the Francois PCT in view of the Ramstack PCT and U.S. Patent No. 5,631,021. For at least the following reasons, Applicants respectfully submit that this rejection cannot properly be maintained.

As explained on page 2, lines 13-21 of the application as originally filed, "[S]yringeability describes the ability of an injectable suspension to pass easily through a hypodermic needle on transfer from a vial ***prior to injection***" and "[I]njectability refers to the performance of the suspension ***during*** injection" (emphases added). Thus, the specification makes clear that syringeability only considers the ability of the suspension to pass through a needle and does not consider whether the suspension can be injected into a host. The

performance of the suspension during the injection, whether it can be actually injected from the needle into a host, is injectability, not syringeability. That a suspension can be syringeable but not injectable is demonstrated, for example, by the data for Vehicle A in Table 4 of the application as originally filed. As explained on page 16, lines 7-16 of the application as originally filed, the suspensions of Table 4 were successfully aspirated from a vial into the syringe using a 22 gauge needle. Thus, the suspension of Vehicle A in Table 4 is syringeable. The suspensions of Table 4 were then injected into a host animal. The Vehicle A suspension (having a viscosity of the fluid phase of only 1.0 cp) experienced 8/10 injection failures, demonstrating that, although syringeable, it was not injectable.

As explained on page 2, lines 17-18 of the application as originally filed, conventional teaching prior to the present invention as described in the Floyd *et al.* chapter, is that an increase in the viscosity and concentration of solids in the suspension hinders the syringeability of suspensions. Moreover, as explained on page 4, lines 7-8 of the application as originally filed, a higher concentration of solids makes it more difficult to successfully inject microparticle suspensions. Contrary to the conventional teaching, the inventors of the present invention have unexpectedly discovered that high concentration suspensions can be successfully injected into a host by increasing the viscosity used with the high concentration suspension.

Each of the independent claims requires injectability into a host of a suspension having a concentration in the range of from about 175 mg/ml to about 400 mg/ml, with the viscosity of the fluid phase of the suspension being in the range of from about 20 cp to about 600 cp at 20°C. Independent claims 1, 18, 29, and 33 have been amended herein to more clearly recite that the claimed invention provide provides injectability into a host. The Francois PCT provides no disclosure or suggestion of ***injectability*** of such a suspension, and teaches one skilled in the art away from the claimed invention.

Although the Francois PCT provides a couple of examples of ***syringeability*** of the compositions, only one example is provided of ***injectability*** of the compositions. In particular, page 10 of the Francois PCT explains that for Formulation 4 (F4), having a concentration of 7.8% (or 78 mg/ml), "***syringeability*** through a 22 G 1 ¼ needle posed no problem." (emphasis added) Similarly, page 11 of the Francois PCT explains that Formulas 5a, 5b and 5c, having a

concentration and suspension viscosity of 15.6% (156 mg/ml) and 12 mPa.s, 23.4% (234 mg/ml) and 16 mPa.s, and 31.2% (312 mg/ml) and 16 mPa.s, respectively, were ***syringeable*** through a 22 G 1 ¼ needle.

The one example in the Francois PCT regarding injectability is provided on page 11, lines 18-32, wherein F1 was administered intramuscularly at 2.5 mg/kg bodyweight to four beagle dogs using a 21 G needle. As explained on page 9 of the Francois PCT, Formulation F1 has a concentration of 15.6% (156 mg/ml) and a suspension viscosity of 20 mPa.s. The foregoing makes clear that the Francois PCT provides no teaching to one skilled in the art of injectability into a host of a suspension having a concentration in the range of from about 175 mg/ml to about 400 mg/ml, with the viscosity of the fluid phase of the suspension being in the range of from about 20 cp to about 600 cp at 20°C as claimed in each of the independent claims. Because neither the Francois PCT, nor any of the other documents cited by the Examiner, provides any teaching or suggestion of the invention as claimed, Applicants respectfully submit that the rejection cannot properly be maintained.

The Examiner asserts on pages 6 and 9 of the Office Action that "it would have been obvious to one of ordinary skill in the art to, by routine experimentation determine a suitable microparticles [sic] concentration to obtain an injection composition that provides injectability through a needle of medically acceptable size." To determine a suitable concentration and suspension that provides injectability into a host, one skilled in the art would be guided by the conventional teaching described in the Floyd *et al.* chapter that an increase in the viscosity and concentration of solids in the suspension hinders the syringeability of suspensions, and a higher concentration of solids makes it more difficult to successfully inject microparticle suspensions.

Moreover, the Francois PCT teaches one skilled in the art to solve syringeability problems by decreasing viscosity. As noted on page 5, lines 24-25 of the Francois PCT, because oil suspensions proved difficult to take up in a syringe, experiments with ***less*** viscous carriers were initiated. Therefore, one skilled in the art starting with the examples of the Francois PCT would be guided to ***decrease*** both the viscosity and concentration from the examples shown in the Francois PCT. One skilled in the art would have no reason based on conventional teachings of the Floyd *et al.* chapter and the Francois PCT itself to increase the viscosity and concentration

in an attempt to achieve an injectable composition. The Francois PCT and the Floyd *et. Al* chapter both teach one skilled in the art away from the invention as claimed. One skilled in the art would have no reason to increase the concentration or viscosity of Formula F1 of the Francois PCT given the teachings that doing so would hinder both syringeability and injectability, and would have no reasonable expectation that doing so would result in a syringeable, much less an injectable, suspension.

For at least all of the foregoing reasons, Applicants respectfully submit that the rejection cannot properly be maintained because the documents cited by the Examiner: provide no teaching or disclosure of a suspension injectable into a host with the concentration and viscosity ranges as claimed in each of the independent claims; provide no reason for one skilled in the art to make the modifications suggested by the Examiner; teach one skilled in the art away from the modifications suggested by the Examiner; and provide no reasonable expectation of success for a suspension injectable into a host having the claimed concentration and viscosity ranges. As such, Applicants respectfully request the Examiner to withdraw the rejection, and pass the application to issue.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Dated: October 26, 2007

Respectfully submitted,

By _____
Andrea G. Reister
Registration No.: 36,253
COVINGTON & BURLING LLP
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004-2401
(202) 662-6000
Attorney for Applicant